QP171 Sa52
Columbia University
in the City of New York
College of Physicians and Surgeons

Library

Digitized by the Internet Archive
in 2010 with funding from
Open Knowledge Commons (for the Medical Heritage Library project)

http://www.archive.org/details/clinicalmetaboli00sand

CLINICAL METABOLISM

THE BASAL METABOLIC RATE IN EXOPHTHALMIC GOITRE (1917 CASES) WITH A BRIEF DESCRIPTION OF THE TECHNIC USED AT THE MAYO CLINIC

THE EFFECT OF THE SUBCUTANEOUS INJECTION OF ADRENALIN CHLORID ON THE HEAT PRODUCTION, BLOOD PRESSURE AND PULSE RATE IN MAN

BY

IRENE SANDIFORD

A THESIS

Submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the Degree of Doctor of Philosophy

1919

QP171
Sa52

Ex. Univ. of Illinois.
10/7/20

THE BASAL METABOLIC RATE IN EXOPHTHALMIC GOITRE (1917 CASES) WITH A BRIEF DESCRIPTION OF THE TECHNIC USED AT THE MAYO CLINIC

Irene Sandiford, Ph.D.

Mayo Foundation, University of Minnesota, Rochester, Minnesota

"In each mammal there is a basal metabolism" (19). By the term "basal metabolism" or better, "basal metabolic rate," of an organism is meant the minimal heat production of that organism, measured from twelve to eighteen hours after the ingestion of food and with the organism at complete muscular rest. This minimal heat production may be determined directly by actual measurement by means of a calorimeter, or indirectly, by calculating the heat production from an analysis of the end products which result from oxidation within the organism, or specifically, from the amount of oxygen used and the corresponding amount of carbon dioxid produced, together with the total nitrogen eliminated in the urine (although, for clinical work the urinary nitrogen may be neglected).

The experimental work of Lavoisier (17) marks the beginning of researches on metabolism, and to him belongs the conception that the life processes are those of oxidation with the elimination of heat. Technically, the problem was beset with many difficulties, for it was necessary not only to measure the amount of heat lost by radiation and conduction from the body (direct calorimetry), but also to collect accurately the various end products resulting from combustion within the body, from which data the heat production can be calculated (indirect calorimetry), in order to prove from a comparison of the results obtained from the two methods that the law of conservation of energy also holds for the living organism. Furthermore, before the method of indirect calorimetry could be employed the heat values of carbohydrate, fat, and protein had also to be determined in order to calculate the heat derived from their combustion in the body. The solution of these problems was greatly advanced by Carl Voit (23) and his pupils, the chief of whom

Reprinted from Endocrinology, 1920,
IV, No. 1, January--March, 71-87

were Pettenkofer (22) and Rubner (27). The heat values of carbohydrate and fat were readily determined by Rubner (25) since these two substances are oxidized to the same end products (carbon dioxid and water) whether burning in the body or in a calorimeter. In the case of protein, however, the problem was somewhat more difficult, for a part of the end products of protein combustion in the body is eliminated in the urine and feces and the latent heat thereby lost had to be subtracted from the heat value of protein as determined in the calorimeter.

In 1894 Rubner (26) constructed the first successful respiration calorimeter designed for the measurement of the gaseous exchange between a living organism and the atmosphere which surrounds it and the simultaneous measurement of the quantity of heat produced by that organism. By means of this apparatus Rubner verified the method of Pettenkofer and Voit of calculating the heat production (indirect calorimetry) and he proved that the law of conservation of energy holds for the living organism.

It was not until 1905 that the respiration calorimeter was brought to a high degree of technical perfection by Atwater and Benedict (1). With their apparatus it was possible to determine simultaneously with the measurement of the heat elimination, not only the carbon dioxid production, but also the oxygen consumption of the subject. Studies made by Benedict and his associates, at the Carnegie Nutrition Laboratory, using the perfected calorimeter, have added greatly to the exactness of our knowledge with regard to the metabolism in prolonged fasting (4), the metabolism of normal persons (6), of infants (8), and of diabetics (7). They also confirmed the agreement between direct and indirect calorimetry. Lusk (18) and Du Bois and their co-workers have likewise demonstrated, in a large series of pathologic conditions, the close agreement between the two methods. As a result of these investigations the use of such a complicated apparatus as the respiration calorimeter has been shown to be unnecessary for clinical work and that in its place the comparatively simple method of indirect calorimetry may be used.

Krogh (16) of Copenhagen, and Carpenter (11) of the Carnegie Nutrition Laboratory, have described and compared in

great detail the various kinds of respiration apparatus used in indirect calorimetry. Carpenter has shown that for indirect determinations two types of apparatus are suitable, the closed circuit and the gasometer.

By far the best apparatus of the closed circuit type is the Benedict unit apparatus (2). By means of a mask, mouthpiece or nasal tubes, the subject rebreathes air from a closed system in which the carbon dioxid is absorbed by soda lime, and, as the oxygen is used up, it is replaced by oxygen in known amounts. The air within the apparatus is kept in constant circulation by means of a blower. A small spirometer is inserted in the circuit as an expansion chamber and volumetrically records the respiratory movements on a smoked drum. Knowing the weights of oxygen used and the carbon dioxid eliminated, one can readily calculate the heat production. As pointed out by Carpenter, this apparatus is very satisfactory and indeed the best for many purposes, especially when used in conjunction with a calorimeter or with the cot-chamber calorimeter described by Benedict and Tompkins (9). We have found, however, that for clinical work the unit apparatus is rather cumbersome. It requires constant checking to see that it is absolutely air tight, for a leak of 20 or 30 c.c. during a fifteen minute determination will appreciably affect the result, because such a leak in this type of apparatus will be equivalent to the loss of so much oxygen and not equivalent to the loss of so much air as is the case in the gasometer method. Furthermore, the accumulation errors of the apparatus fall on the oxygen and not on the carbon dioxid determination, thus causing an error in the calculation of the respiratory quotient and heat production. The absorbing chemicals must be changed frequently and with the repairing and constant checking of the apparatus it is on the whole difficult to use in clinical work, particularly if many determinations are to be made.

The portable respiration apparatus recently devised by Benedict (5) for clinical work is a modification of his unit apparatus described above. It is designed primarily to give a rapid and at the same time a comparatively accurate measurement of the oxygen consumption without involving analyses or weighing. We have not adopted it, as we prefer to determine not only the

oxygen consumption, but also the carbon dioxid elimination since the heat production can thereby be more accurately calculated. Moreover, the difficulties inherent in the closed circuit type of apparatus are still present in the portable apparatus.

For clinical work the gasometer method introduced by Tissot (29) in 1904 is considered by us the most satisfactory. Briefly, the determinations are made in the following manner: A mask is adjusted over the patient's mouth and nose and by means of expiratory and inspiratory valves the total volume of the patient's expired air is collected in a gasometer for a known period of approximately ten minutes. Duplicate determinations are made of the carbon dioxid and oxygen content of the expired air, the analyses being done in the Haldane gas analysis apparatus (14). Since the ventilation rate for each minute is known, as well as the amount of carbon dioxid produced and the oxygen absorbed, it is possible to calculate by means of calorie tables the total number of calories produced each hour.

The following points in the routine determination of the basal metabolic rate deserve further discussion: To obtain comparable results the patient must be in the postabsorptive condition, that is, he must fast for at least twelve hours preceding the test. It is very important that this rule should be observed, because all kinds of foods cause an increase in the heat production and this effect may not entirely disappear for twelve hours after their ingestion (28). Moreover, the patient must be at complete rest and the effects of previous muscular exertion eliminated by requiring him to rest in bed for twenty minutes before the test is started, for we have shown in a series of experiments that a rest period of this length of time is quite sufficient to obtain the basal metabolism (10). During the preliminary rest period an observer sits with the patient, noting at intervals the character and rate of the heart beat and the respiration; likewise, about the middle of the period, the blood pressures, both systolic and diastolic, are obtained. After twenty minutes' rest a mask is accurately adjusted over the nose and mouth of the patient and securely held in place by means of tapes so that there is no leakage of air around the mask (Fig. 1). A mask is preferable to either a mouthpiece or nasal tubes. With a little experience it is possible to adjust the mask

so that it is not only comfortable for the patient, but also air-tight. One of the chief advantages of the gasometer method is that should a very slight leak of a few cubic centimeters occur around the mask during the course of an experiment the end

Fig. 1. Mask and connections showing valves, intake pipe and towel with tapes.

result is not appreciably affected, while a leak of a similar volume in the closed circuit apparatus has a value at least five times as great, because in the latter case it is equivalent to the loss or gain of so much pure oxygen.

During the test proper the observer sits with the patient, recording his pulse and respiration rates and noting and recording on a special chart any movements. Care is taken to impress on the patients that even slight movements materially affect the

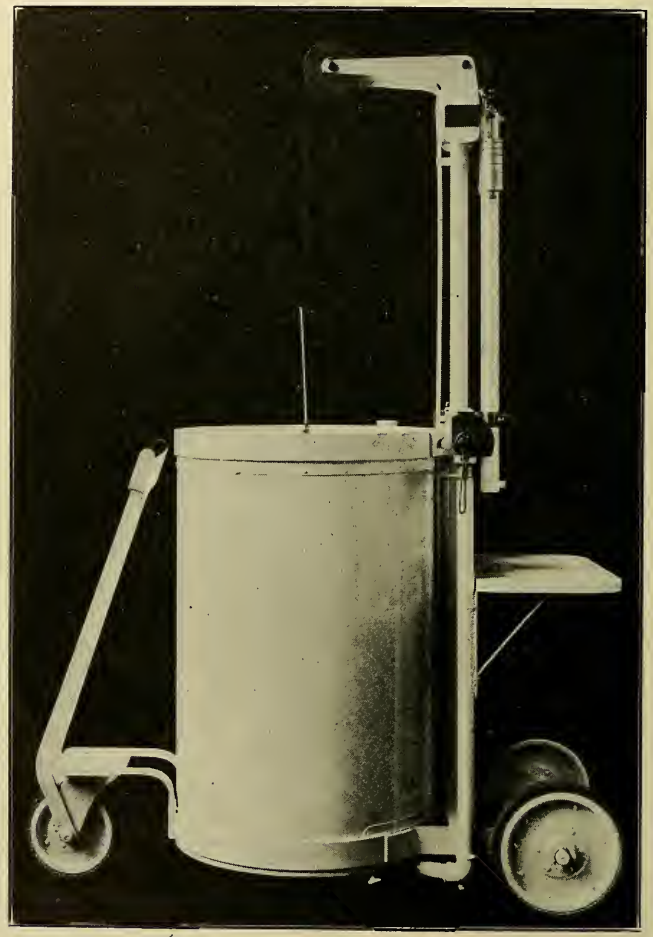

Fig. 2. Moveable gasometer.

test and it is almost always possible to obtain their complete co-operation. Sometimes, however, in an extremely nervous person, a basal rate cannot be obtained on the first test. Instead of repeating the determination the same day the patient is in-

structed to return the following morning for a second test. In such instances the rate will occasionally be ten points lower than that obtained the first time when the patient was unduly nervous and frightened about an unknown procedure.

The total volume of the expired air is collected in a gasometer (Fig. 2) over a known length of time. Unlike in the work with the closed circuit apparatus no appreciable error is introduced by failing either to start or stop the experimental period at exactly the end of a normal respiration, a difficult thing to do with accuracy in the case of patients who breathe irregularly. Samples of the expired air are then collected over mercury in sampling tubes and analyzed in duplicate for carbon dioxid and oxygen. Approximately 10 c.c. of expired air are transferred into the burette of the Haldane gas analysis apparatus (Fig. 3) and after adjusting certain levels the reading of the initial volume of the sample is made, reading to the nearest 0.001 c.c. The gas sample is then passed back and forth over a solution of dilute potash to absorb the carbon dioxid. The levels of the solution are again adjusted and a second reading of the volume of the remaining gas in the burette made. The contraction in volume of the gas, due to the absorption of the carbon dioxid by the potash solution, divided by the original volume, gives the percentage of carbon dioxid in the expired air. In like manner the percentage of oxygen is determined, potassium pyrogallate solution being used as the absorbent for oxygen.

The gasometer method is particularly suitable for clinical work because each step in the procedure can be checked by a second assistant, reducing to a minimum the chance of technical errors. Although the method requires care and accuracy in every part of the procedure, it is possible to teach the technic to laboratory workers who have had no preliminary scientific training other than that obtained in a high school. The most difficult step in the procedure is the analysis of the expired air. This, however, we have found to be inconsiderable. Our assistants can obtain routinely duplicate analyses agreeing within 0.04 per cent for carbon dioxid and 0.06 per cent for oxygen, and they are able also to take entire care of their gas analysis apparatus. The equipment necessary for this method is simple and inexpensive and when properly constructed

is rarely out of order and, except for cleaning, requires very little mechanical care. Furthermore, the apparatus is free from the many mechanical difficulties inevitably inherent in a closed circuit system in which the air current is driven by an electric

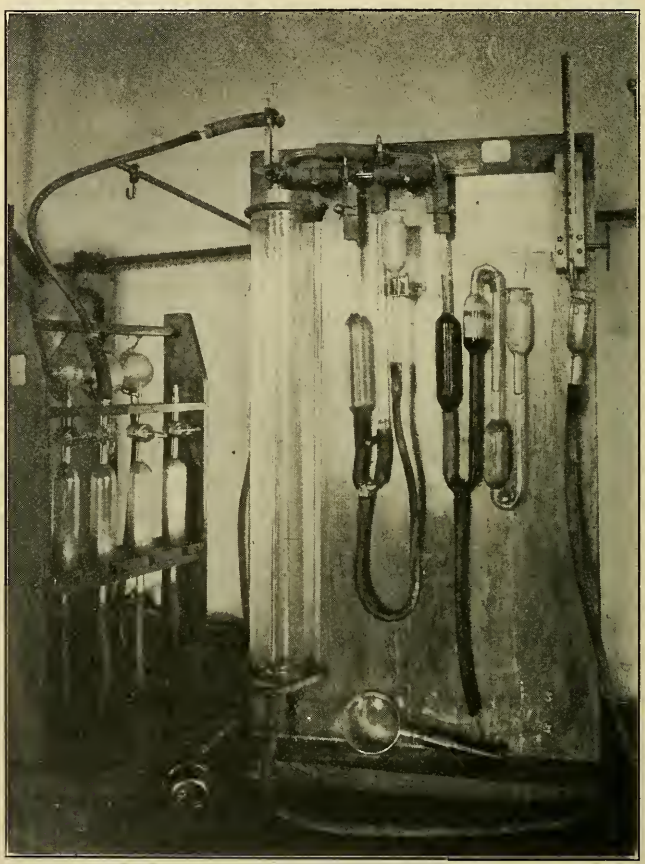

Fig. 3. Haldane gas analysis apparatus.

pump. In the metabolism laboratory at the Mayo Clinic we are averaging 30 cases a day and have developed a very definite and routine procedure which has decreased the chance of technical error to less than 1 per cent.*

* The details of the technic are described in a laboratory manual by Boothby and Sandiford (10). The apparatus may be obtained from H. N. Elmer, 1136 Monadnock Bldg., Chicago.

The calculation of the basal metabolic rate from the experimental data is very simple. Knowing the volume of air expired by the patient in a minute (the ventilation rate) and the percentage of carbon dioxid and oxygen in the expired air, it is possible to calculate the volume of oxygen absorbed by the patient in one hour, as well as the corresponding amount of carbon dioxid produced. Since the respiratory quotient, that is the ratio between the volume of carbon dioxid produced and the volume of oxygen absorbed, indicates the kind of food being burned at the time of the determination, and since by means of calorie tables the calorific value of one liter of oxygen absorbed by the body in the burning of these substances is known, the total heat production each hour can be calculated readily. The total number of calories must be divided by the surface area, a factor dependent on the patient's height and weight. The number of calories for each square meter of body surface each hour must then be compared with the normal standards of comparison which are dependent on the age and sex of the patient. For convenience, basal metabolic rates are expressed in percentages of the normal, and when the heat production is greater than the normal the percentage is plus, and when less than normal the percentage is minus.

A very important contribution was made by Du Bois (12, 13) in determining the heat production in normal controls. Rubner (24) had suggested that the heat production of an individual is proportional to his surface area. For the determination of the surface area Meeh (21) proposed the formula: Surface area in square centimeters=12.3 (a constant) $\times$ weight in grams$^{\frac{2}{3}}$. However, using the surface area obtained by this formula as a basis of comparison, the heat production of normal controls still showed quite wide variations, although not so great as when compared on the basis of weight alone. By exact measurements of the surface area of several bodies Du Bois demonstrated an error in the above formula due in greater part to the fact that the height of the subject was neglected. As a result of further studies Eugene F. Du Bois and Delafield Du Bois (12, 13) devised a formula based on height

and weight by means of which the surface area can be calculated with an average error of 1.7 per cent. This formula is:

$$A = W^{0.425} \times H^{0.725} \times 71.84$$

Where A is the surface area in square centimeters, W is the weight in kilograms and H is the height in centimeters, and 71.84 is a constant. On the basis of this formula they then constructed a height-weight chart by means of which the surface area can be estimated at a glance. Du Bois (12, 13), using this new height-weight chart for the determination of the surface area in conjunction with his standards of normal basal metabolism with regard to age and sex, further showed that the metabolism of normal persons can be predicted with an accuracy of ± 10 per cent. This fact has been confirmed both by Means (20) and by Boothby (19). Benedict (3) has severely criticized the method of predicting the heat production from the unit of surface area, maintaining "that the metabolism or heat output of the human body, even at rest does not depend on Newton's law of cooling, and therefore, is not proportional to the body surface." Harris and Benedict (15) in a very exhaustive treatise have reconsidered the entire problem of the prediction of the normal basal metabolic rate and show that by proper biometric formulas based on stature, body weight, and age (the same factors used by Du Bois), "results as good as or better than those obtainable from the constant of basal metabolism per square meter of body surface can be obtained by biometric formulas involving no assumption concerning the derivation of surface area, but based on direct physical measurements." Since their publication there has not been sufficient time to study in detail the fundamental accuracy of the two methods of prediction; we have, however, tabulated 404 determinations of the basal metabolic rate expressed in percentages above and below normal, using both the standards of Du Bois and of Harris and Benedict. The average rates of all the cases show that the rates obtained by Harris and Benedict's method are 6.5 points higher than those obtained by Du Bois' method. The parallelism between the results obtained by the two methods is strikingly shown by the fact that 195 of the 404 determinations are within ± 2.5 of the average variation. Only 52 of the entire 404 rates deviate

more than 7.5 from the average variation. The comparative agreement, therefore, of the two methods is very satisfactory, indicating as it does the similarity of both methods of comparison, and supporting in a high percentage of the cases the clinical conclusions based on the Du Bois and Du Bois height-weight chart and the Du Bois normal standards for comparison.

The metabolism laboratory at the Mayo Clinic was opened, in March, 1917 by Boothby and Sandiford, under the clinical direction of Dr. H. S. Plummer, and in that year 1143 metabolic rates were determined on 549 patients. At that time the number of cases that could be studied in the laboratory in proportion to the number of thyroid cases at the clinic was relatively small. In consequence, considerable care was taken by Dr. Plummer to select typical cases of the various groups of thyroid disorders and with his permission this analysis of the metabolic rates in the exophthalmic goitre cases studied during 1917 is presented.

The basal metabolic rate is of the greatest value in thyroid disorders because it gives a very accurate mathematical index of the degree of functional activity of the thyroid gland. For example, in exophthalmic goitre the metabolic rate may rise well over 100 per cent above normal while in myxedema, with apparently complete cessation of thyroid activity, the rate falls to the region of 40 per cent below normal. In the milder cases of both groups the metabolic rate variations from the normal are proportionately smaller. On the other hand, beside thyroid disorders, there are no diseases that have so far been shown to have a constant and distinct variation from the normal in the basal metabolic rate except disorders of the pituitary gland, conditions of profound inanition, and fevers. However, an occasional case is met with in which there is a variation in the basal metabolic rate that at present cannot be explained or properly classified. Such variations are more frequent in patients with considerable evidence of nephritis or anemia. No definite instance of an increased basal metabolic rate has been found in that group of cases known as neurasthenia or chronic nervous exhaustion. The basal metabolic rate has proved, therefore, to be of great value

in the differential diagnosis of neurosis simulating hyperthyroidism and true hyperthyroidism.

In 182 cases of exophthalmic goitre before any treatment was instituted the average metabolic rate was +51 per cent, with an average pulse rate of 115. In 13 patients whose average metabolic rate, as outpatients, was +59 per cent, with an average pulse rate of 115, the average metabolic rate fell to +46 per cent, and the average pulse rate to 108 as a result of approximately one week's complete rest in bed. In 5 patients whose average metabolic rate, determined within two to five days after they entered the hospital, was +59 per cent and the pulse 118, after a further rest in bed of approximately one week's duration there was a definite improvement in their condition, as shown by a fall in the metabolic rate to an average of +48 per cent and pulse to 104.

The effect of a single ligation was studied in 16 cases. The basal metabolic rate taken after the patient had had several days' rest in bed and within five days before the first ligation was +54 per cent and the pulse 116. One week after the single ligation the average metabolic rate had decreased to +44 per cent and the pulse to 112.

The immediate result of ligation or thyroidectomy in hyperthyroidism is to cause at first a rise in the metabolic rate for a few days, followed by a gradual fall to a distinctly lower level on the average than that obtained preceding the operation. The curve of the basal metabolic rate on the average roughly parallels the pulse rate curve. The former is, however, a far more accurate index of the degree of hyperthyroidism than is the pulse rate, as the latter shows more individual and extraneous variations, for example, the irregularities of auricular fibrillation.

The effect of the second ligation is likewise a general improvement in the patient's condition as evidenced by a decrease in the metabolic rate. An average figure of any value on the immediate result of the second ligation in the patients in the 1917 series cannot be given, as practically no rates were obtained in the same case immediately preceding and following the second ligation. There is a very marked improvement in these patients when they return for their thyroidectomy

two to four months after the second ligation. In 22 patients (Table 1) there was an average decrease in the basal metabolic rate from +46 per cent to + 39 per cent, and in the pulse from 115 to 107 with a gain in weight from 46.4 to 54.5 kilograms in the determinations made a few days after the second ligation as compared with the data obtained after three months' rest at home and just previous to thyroidectomy. From the clinical history it is probable that the basal metabolic rate determined at the time the patients returned for operation after having had two ligations and three months' rest at home may not necessarily represent in all cases the period of maximum improvement produced by the two ligations and rest. A definite improvement from thyroidectomy in those patients who had had two ligations and a three months' rest was shown two weeks following operation by a decrease in the basal metabolic rate from +39 per cent to +16 per cent, and in the pulse rate from 107 to 89.

In another group of 19 patients (Table 2) with exophthalmic goitre in whom the preliminary basal metabolic rate varied between +13 per cent and +50 per cent, giving an average of +31 per cent with an average pulse rate of 104, and in whom a primary thyroidectomy was done without any other preliminary treatment, except for a short rest in bed, the basal metabolic rate fell, about two weeks after operation, to +5 per cent and the pulse to 84.

The general effect of the treatment adopted at the Mayo Clinic for severe cases of exophthalmic goitre may be illustrated, then, by the following data: In a group of 22 patients (Table 1) the average basal metabolic rate, before any treatment was instituted, was +66 per cent, with a pulse rate of 123. As a result of rest in bed and two ligations the rate in these patients before they went home had decreased to +46 per cent and the pulse to 115. The further improvement that occurred from three months' rest at home reduced the average metabolic rate to +39 per cent and the pulse rate to 107 and finally, after thyroidectomy and just before the patients were discharged from

As will be noted, following thyroidectomy there is almost always a marked decrease in the basal metabolic rate within the clinic, the rate was +16 per cent and the pulse 89.

Table 1

THE EFFECT OF TWO LIGATIONS AND THYROIDECTOMY ON THE BASAL METABOLIC RATE IN EXOPHTHALMIC GOITRE

	Before treatment			Within five to nine days after second ligation			Three months after second ligation			Ten to thirty days after thyroidectomy		
Case	Wt. kg.	Pulse	B.M.R. Per cent	Wt. kg.	Pulse	B.M.R. Per cent.	Wt. kg.	Pulse	B.M.R. Per cent.	Wt. kg.	Pulse	B.M.R. Per cent.
208970	50.1	139	+101	38.1	118	+36	52.2	95	+50	56.8	69	+15
201022	48.5	175	+ 98	40.9	124	+49	51.5	114	+26	48.1	107	+ 6
196042	46.0	138	+ 93	45.6	126	+61	53.3	104	+43	51.9	91	+20
197894	46.7	128	+ 77	39.5	129	+46	58.4	113	+13	56.5	105	+ 1
192274	27.3	138	+ 76	40.1	120	+53	42.7	129	+58	40.9	92	+27
194824	42.4	127	+ 76	41.6	123	+58	51.9	110	+34	51.4	100	+13
210160	54.9	131	+ 75	57.7	124	+60	63.9	105	+55	63.0	82	+21
196845	49.7	129	+ 74	47.5	146	+78	55.3	129	+68	56.0	120	+58
215648	42.1	117	+ 73	43.4	115	+54	48.0	82	+12	53.7	74	− 6
202677	60.5	98	+ 65	58.4	96	+34	64.1	94	+55	61.9	86	+34
191713	49.0	87	+ 65	43.5	83	+45	50.5	90	+62	50.5	71	+49
187927	48.5	121	+ 63	45.0	117	+43	49.4	112	+53	48.6	70	+ 3
189311	60.7	141	+ 60	49.9	88	+27	58.3	105	+43	56.0	44	0
199039	43.1	121	+ 56	36.6	123	+50	48.2	100	+50	48.6	76	+14
200063	46.5	95	+ 55	45.9	110	+58	46.9	121	+54	46.6	97	+20
199909	46.0	134	+ 55	46.0	127	+42	52.8	132	+52	53.0	88	+13
136490	55.1	107	+ 55	44.2	104	+41	65.5	82	+11	65.3	85	0
194306	43.2	126	+ 53	42.0	124	+48	50.1	117	+21	49.5	105	+ 9
197356	58.5	99	+ 52	53.0	80	+13	60.0	77	+ 1	56.9	75	− 2
191257	60.5	130	+ 50	56.7	123	+45	61.2	110	+34	58.5	117	+16
209717	55.6	133	+ 47	54.0	141	+37	59.0	127	+39	57.0	88	+16
190576	53.0	86	+ 31	51.6	92	+31	55.6	106	+25	58.3	106	+19
Average	49.5	123	+ 66	46.4	115	+46	54.5	107	+39	54.0	89	+16

two weeks after the operation and, as a rule, there is still further improvement in the succeeding months, just as is seen to occur in the interval after the second ligation. Occasionally, a varying degree of hyperthyroidism may persist, as shown by

Table 2

THE EFFECT OF PRIMARY THYROIDECTOMY ON THE BASAL METABOLIC RATE IN EXOPHTHALMIC GOITRE

	Before treatment		About two weeks after operation	
Case	Pulse	B. M. R. Per cent	Pulse	B. M. R. Per cent
214581	88	+50	70	+19
196806	109	+45	93	+ 3
202992	107	+45	92	+ 5
200219	145	+42	115	+12
201229	102	+40	75	+14
202481	105	+39	68	+ 1
202527	112	+36	92	+15
194686	97	+35	75	+ 1
212298	108	+34	91	+ 5
202232	113	+32	118	+32
203326	127	+30	89	+10
3396	101	+29	83	+13
198725	99	+27	67	0
196664	79	+21	58	−11
203291	87	+18	73	− 6
199740	95	+18	69	− 7
217150	99	+16	85	− 5
215895	118	+16	98	− 9
208637	89	+13	84	+ 6
Average	104	+31	84	+ 5

an elevated basal metabolic rate. In these cases a second (and rarely a third) thyroidectomy is indicated.

BIBLIOGRAPHY

1. Atwater, W. O., and Benedict, F. G.: A respiration calorimeter with appliances for the direct determination of oxygen. Carnegie Inst., Washington, 1905, Pub. No. 42.
2. Benedict, F. G.: Ein Universalrespirationsapparat. Deutsch. Arch. f. klin. Med., 1912, **107**, 156.
3. Benedict, F. G.: Factors affecting basal metabolism. Jour. Biol. Chem., 1915, **20**, 263-313.
4. Benedict, F. G.: A study of prolonged fasting. Carnegie Inst., Washington, 1915, Pub. No. 203.

5. Benedict, F. G.: A portable respiration apparatus for clinical use. Boston Med. and Surg. Jour., 1918, **178**, 567.
6. Benedict, F. G. and Carpenter, T. M.: Metabolism and energy transformation of healthy man during rest. Carnegie Inst., Washington, 1910, Pub. No. 126.
7. Benedict, F. G., and Joslin, E. L.: Metabolism in diabetes mellitus. Carnegie Inst., Washington, 1910, Pub. No. 136.
A study of metabolism in severe diabetes. Carnegie Inst., Washington, 1912, Pub. No. 176.
8. Benedict, F. G., and Talbot, F. B.: The gaseous metabolism of infants. Carnegie Inst., Washington, 1914, Pub. No. 201.
The physiology of the new-born infant. Carnegie Inst., Washington, 1914, Pub. No. 233.
9. Benedict, F. G., and Tompkins, Edna H.: Respiratory exchange, with a description of a respiration apparatus for clinical use. Boston Med. and Surg. Jour., 1916, **174**, 857.
10. Boothby, W. M., and Sandiford, Irene: Technic of basal metabolic rates determinations. Philadelphia, Saunders, 1920.
11. Carpenter, T. M.: A comparison of methods for determining the respiratory exchange of man. Carnegie Inst., Washington, 1915, Pub. No. 216.
12. Du Bois, D., and Du Bois, E. F.: The measurement of the surface area of man. Clinical calorimetry. Paper V. Arch. Int. Med., 1915, **15**, 868-881.
13. Du Bois, D., and Du Bois, E. F.: A formula to estimate the approximate surface area if height and weight be known. Clinical calorimetry, Paper X. Arch. Int. Med., 1916, **17**, 863-871.
14. Haldane, J. S.: Methods of air analysis. London, Griffin, 1912.
15. Harris, J. A., and Benedict, F. G.: A biometric study of basal metabolism in man. Carnegie Inst., Washington, 1919, Pub. No. 279.
16. Krogh, A.: The respiratory exchange of animals and man (with excellent bibliography). London, Longmans, Green & Co., 1916.
17. Lavoisier, A. L., and Laplace: Mémoire sur la chaleur. Mém. de math. et de phys. de l'Acad. d. Sc., 1780, 355.
Lavoisier, A. L., and Seguin: Premier mémoire sur la respiration des animaux. Mém. de math. et de phys. de l'Acad. d. Sc., 1789, 566. (Also: "Oeuvres de Lavoisier," 1862).
18. Lusk, G.: A series of papers on clinical calorimetry by Lusk and his associates appearing in Arch. Int. Med., beginning in 1915, **15**.
19. Lusk, G.: Science of nutrition. Philadelphia, Saunders, 3 ed., 1917, 641 pp.
20. Means, J. H.: Basal metabolism and body surface. A contribution to the normal data. Jour. Biol. Chem., 1915, **21**, 263-268.
21. Meeh, K.: Oberflächenmessungen des menschlichen Körpers. Ztschr. f. Biol., 1879, **15**, 425-458.
22. Pettenkoffer, M.: Ueber die Respiration. Ann. d. Chem. u. Pharm., 1862, **2**, Suppl. 1.
23. Pettenkoffer, M., and Voit, C.: Untersuchungen über die Respiration. Ann. d. Chem. u. Pharm., 1862, Suppl. 52.
24. Rubner, M.: Ueber den Einfluss der Körpergrösse auf Stoff-und Kraftwechsel. Ztschr. f. Biol., 1883, **19**, 535-562.
25. Rubner, M.: Calorimetrische Untersuchungen. Ztschr. f. Biol., 1885, **21**, 250-334.

26. Rubner, M.: Die Quelle der tierischen Wärme (Comparison of direct and indirect calorimetry). Ztschr. f. Biol., 1894, **30**, 73.
27. Rubner, M.: Die Gesetze des Energieverbrauchs bei der Ernährung. Leipsic, Deuticke, 1902, 426 pp.
28. Soderstrom, G. F., Barr, D. P. and Du Bois, E. F.: The effect of a small breakfast on heat production. Clinical calorimetry, Paper XXVI. Arch. Int. Med., 1918, **21**, 613-620.
29. Tissot, J.: Nouvelle méthode de mésure et d'inscription du débit et des mouvements respiratoires de l'homme et des animaux. Jour. de phys. et de path. gen., 1904, **6**, 688.

ENDOCRINOLOGY

EDITORIAL STAFF

PROF. R. G. HOSKINS, *Editor-in-Chief*, Baltimore

PROF. ISAAC A. ABT.....Northwestern University, Chicago
PROF. LEWELLYS F. BARKER..Johns Hopkins University, Baltimore
PROF. WALTER B. CANNON.....Harvard Medical School, Boston
PROF. HARVEY CUSHING.....Harvard Medical School, Boston
PROF. E. GLEY.....University of Paris
PROF. B. A. HOUSSAY.....University of Buenos Aires
SIR EDWARD SHARPEY SCHAFER.....University of Edinburgh
PROF. SWALE VINCENT.....University of Manitoba, Winnipeg
PROF. FRANK A. HARTMAN.....University of Buffalo
DR. E. C. KENDALL.....Mayo Clinic, Rochester, Minn.
DR. W. H. MORLEY.....Pontiac, Mich.

COLLABORATORS

PROF. T. C. BURNETT.....University of California, Berkeley
DR. G. P. GOÑALONS.....Buenos Aires, Argentine
DR. MURRAY B. GORDON.....Brooklyn
DR. FREDERICK S. HAMMETT.....Philadelphia
DR. WILLIAM HARRISON (Bibliographer).....Detroit
DR. E. R. HOSKINS*.....University of Minnesota, Minneapolis
DR. J. KOOPMAN.....The Hague, Holland
DR. KNUD H. KRABBE.....Copenhagen, Denmark
DR. JOSHUA H. LEINER.....New York
DR. H. LISSER.....San Francisco
DR. KETIL MOTZFELDT.....Christiana, Norway
DR. JOEL RODIQUEZ P.....University of Chile, Santiago
PROF. HECTOR ROSELLO.....Montevidio, Uruguay
PROF. J. P. SIMONDS.....Northwestern University Medical School, Chicago
DR. BURTON T. SIMPSON.....Buffalo
PROF. ARTHUR L. TATUM.....University of Chicago
DR. L. F. WATSON.....Chicago
DR. HOMER WHEELON.....St. Louis
DR. G. VERCELLINI.....St. Paul

* Deceased.

Reprinted form The American Journal of Physiology,
Vol. 51, No. 3, April, 1920

THE EFFECT OF THE SUBCUTANEOUS INJECTION OF ADRENALIN CHLORID ON THE HEAT PRODUCTION, BLOOD PRESSURE AND PULSE RATE IN MAN

IRENE SANDIFORD

From the Mayo Foundation, University of Minnesota, Rochester, Minn.

Received for publication January 22, 1920

The results of previous studies of the effect on the respiratory exchange of the injection of adrenalin chlorid may be briefly summarized: An increase in the respiratory quotient was found by Fuchs and Roth (1), Hari (2), Bernstein and Falta (3), Lusk and Riche (4), (5) and by Tompkins, Sturgis and Wearn (6). La Franca (7), Wilenko (8) and Bernstein (9) found no change. A greater oxygen consumption or calorific output than normal was noted by La Franca (7), Fuchs and Roth (1), Bernstein and Falta (3), Bernstein (9), Lusk and Riche (4), (5), and by Tompkins, Sturgis and Wearn (6); Wilenko (8) found no change in the oxygen consumption and Hari (2) and Jackson (10) found a decrease.

Of these contributions the most important is that of Tompkins, Sturgis and Wearn (6). In a carefully controlled series of 34 experiments they obtained, without exception, an increase in the heat production following the injection of adrenalin chlorid (0.5 cc. of 1/1000) and this increase was usually accompanied by a rise in the respiratory quotient (27 experiments). Soldiers were studied; they were divided into three groups: *a*, Those with "irritable heart;" *b*, those with hyperthyroidism; and *c*, normal men, that is, well-trained active soldiers on full duty. There were 25 soldiers with "irritable heart," in 13 of whom the increase in the metabolism from the adrenalin injection was accompanied by an increase in the pulse rate and systolic blood pressure of at least ten points each, while in 12 there was a less marked increase. In the 3

... subcutaneous injection of adrenalin chloride on the blood pressure, pulse rate, respiration rate, ventilation rate, respiratory quotient, total calories per hour and basal metabolic rate (standard dose of adrenalin chlorid 0. 5 cc.)

GROUP	CASE	DIAGNOSIS	SEX	AGE	WEIGHT	HEIGHT	BLOOD PRESSURE					PULSE RATE			TOTAL CALORIES PER HOUR			R. Q.		METABOLIC RATE		RESPIRATION RATE		VENTILATION RATE		NOTES
							Basal		Highest																	
							Systolic	Diastolic	Systolic	Diastolic	Percentage increase over basal in systolic	Basal	Highest	Percentage increase over basal	Basal	Highest	Percentage increase over basal	Basal	Highest	Basal	Highest	Basal	Highest	Basal	Highest	
					kgm.	*cm.*																				
1	263084*	Exophthalmic goiter	M	28	57.6	176.4	154	70	165	70	7	121	128	6	137.6	143.3	4	0.75	0.80	+103	+111	23	25	10.06	11.14	Dosage of adrenalin less than standard
	247994*	Exophthalmic goiter	F	36	41.7	157.5	126	76	155	85	23	131	156	19	92.6	113.1	22	0.83	0.95	+85	+126	20	24	6.56	9.31	Dosage of adrenalin less than standard
	259130	Exophthalmic goiter	M	40	67.5	179.1	163	85	178	75	9	118	139	18	125.4	150.7	20	0.77	0.88	+76	+112	22	26	10.60	12.89	
	258885	Exophthalmic goiter	M	34	58.5	178.4	156	72	200	90	28	94	128	36	118.9	161.0	35	0.71	0.91	+74	+136	24	26	9.03	15.22	
	260316	Exophthalmic goiter	M	32	52.3	167.6	136	76	166	80	22	90	118	31	107.0	128.2	20	0.76	0.83	+71	+105	22	26	7.82	10.10	
	262154*	Exophthalmic goiter	F	37	41.4	164.2	136	68	140	70	3	106	135	27	85.3	101.1	19	0.75	0.90	+66	+96	17	26	6.48	8.88	Dosage of adrenalin less than standard
	262154*	Exophthalmic goiter			44.0		120	75	135	78	13	110	129	17	69.4	77.5	12	0.73	0.79	+31	+47	8	10	4.70	5.96	Dosage of adrenalin less than standard; 14 days after thyroidectomy
	258794	Exophthalmic goiter	F	51	43.4	156.9	130	70	155	70	19	123	141	15	77.4	95.3	23	0.75	0.85	+60	+97	16	28	5.71	7.24	
	260358	Exophthalmic goiter	F	26	47.5	162.6	130	64	146	80	12	112	138	23	86.6	97.5	13	0.78	0.88	+58	+78	20	24	6.14	7.94	

2	261849	Exophthalmic goiter	F	24	49.1	163.7	120	72	146	78	22	92	114	24	66.8	79.7	19	0.79	0.86	+20	+43	14	14	4.98	6.27	
	262089	Exophthalmic goiter	M	20	61.1	161.9	128	78	138	85	8	104	112	8	77.4	85.1	10	0.67	0.76	+18	+30	20	22	5.45	7.07	
	262089*	Exophthalmic goiter			59.3		120	78	141	77	18	104	112	8	75.6	90.8	20	0.72	0.82	+17	+40	22	26	5.84	7.39	Thyroxin 5 days previous to this test
	261192	Exophthalmic goiter	F	19	55.5	163.2	120	80	146	68	22	97	107	10	68.2	79.5	17	0.81	0.82	+13	+32	22	32	6.00	7.66	
	261192*	Exophthalmic goiter			55.4		128	80	154	86	20	105	135	29	73.8	88.2	20	0.84	0.96	+22	+46	28	34	7.50	9.38	Thyroxin 5 days previous to this test
	260662	Exophthalmic goiter	M	18	59.9	168.3	116	82	119	76	3	80	80	0	74.9	85.1	14	0.84	0.84	+9	+24	19	16	5.18	6.02	
3	245549	Adenomas of thyroid; hyperthyroidism	M	44	76.1	163.2	135	80	148	82	10	84	144	71	83.9	103.4	23	0.84	0.96	+20	+48	17	16	6.40	8.32	
	245549*	Adenomas of thyroid; hyperthyroidism			74.4		136	65	154	66	13	96	116	21	81.1	97.9	21	0.80	0.93	+16	+41	18	22	5.79	7.98	Thyroxin 7 days previous to this test
	261171	Adenomas of thyroid; hyperthyroidism	F	59	60.5	161.3	152	92	158	76	4	63	79	25	65.3	79.2	21	0.89	0.92	+14	+38	18	19	6.67	7.94	
	262353	Adenomas of thyroid; hyperthyroidism	M	48	73.0	176.5	125	75	145	75	16	86	116	35	82.0	103.9	27	0.77	0.98	+12	+42	15	24	5.67	9.67	

TABLE 1—*Continued*

GROUP	CASE	DIAGNOSIS	SEX	AGE	WEIGHT	HEIGHT	BLOOD PRESSURE					PULSE RATE			TOTAL CALORIES PER HOUR			R. Q.		METABOLIC RATE		RESPIRATION RATE		VENTILATION RATE		NOTES
							Basal		Highest																	
							Systolic	Diastolic	Systolic	Diastolic	Percentage increase over basal in systolic	Basal	Highest	Percentage increase over basal	Basal	Highest	Percentage increase over basal	Basal	Highest	Basal	Highest	Basal	Highest	Basal	Highest	
					kgm.	*cm.*																				
4	119415	Double oöphorectomized neurasthenic; hyperthyroidism	F	21	45.5	164.4	114	74	130	70	14	74	112	51	62.7	83.2	33	1.06	1.17	+15	+53	16	22	6.72	12.10	
5	287796	Adenomas of thyroid without hyperthyroidism	F	30	59.5	174.9	125	75	118	74	−6	82	104	27	65.4	72.3	11	0.71	0.77	+4	+15	18	18	5.57	6.64	
6	256032	Colloid goiter; hypothyroidism	F	17	47.2	153.7	116	70	132	80	14	62	78	26	48.0	61.6	28	0.90	0.88	−16	+9	15	20	3.69	5.20	
7	262125	Addison's disease?	F	32	53.7	170.2	98	70	104	80	6	100	95	−5	57.3	66.3	16	0.82	0.80	−3	+12	14	16	5.34	5.63	
	261437	Addison's disease?	F	35	32.2	158.1	80	58	86	52	8	94	99	5	41.3	47.9	16	0.83	0.80	−8	+7	17	17	4.20	5.01	

8	285194	Hypopituitarism	M	33	79.5	193.4	122	86	132	90	8	64	91	42	77.7	93.2	20	0.77	0.97	−6	+13	8	13	5.05	6.99	
	261342	Hypopituitarism	M	33	67.4	177.8	90	64	96	62	7	62	68	10	63.4	72.0	14	0.72	0.77	−13	−1	16	18	4.58	6.17	
	261342*	Hypopituitarism			64.7		116	78	118	66	2	58	90	55	68.2	82.9	22	0.65	0.85	−5	+16	16	18	4.20	7.00	Thyroxin 6 days previous to this test
	276369	Hypopituitarism	M	44	62.8	173.2	90	60	88	64	−2	57	64	12	48.0	52.2	9	0.82	1.04	−28	−22	12	18	4.61	6.61	
9	262555	Myxedema	M	39	64.0	179.7	114	88	122	70	7	60	59	−2	42.9	47.2	10	0.83	0.85	−40	−34	10	13	3.25	3.66	
	262555*	Myxedema			59.2		128	80	160	90	25	64	79	23	64.4	79.2	23	0.79	0.88	−7	+15	16	18	5.06	6.23	Thyroxin 7 days previous to this test
	262235	Myxedema	F	49	68.6	160.6	120	90	132	85	10	73	76	4	43.5	48.0	10	0.82	0.81	−30	−23	10	9	2.74	3.06	
	259013*	Myxedema	F	46	84.7	155.6	104	68	124	66	19	87	98	13	65.8	78.5	19	0.74	0.82	−1	+19	22	30	5.90	8.05	Thyroxin 19 days previous to this test
10	61699	Postoperative myxedema	F	41	54.1	163.2	130	86	112	80	−14	70	76	9	49.5	60.5	22	0.93	1.06	−13	+7	17	9	3.91	5.19	
	137062	Postoperative myxedema	F	37	74.5	162.6	118	90	135	90	14	77	88	14	54.2	73.7	36	0.79	0.85	−18	+12	17	19	4.33	6.52	
11	257217	Atypical hypothyroidism on thyroxin	M	56	52.3	173.4	122	68	132	68	8	65	96	48	66.7	94.5	42	0.78	0.89	+10	+55	14	17	4.73	6.58	
12	276977	Anorexia nervosa; hypothyroidism	F	16	37.8	170.6	80	58	104	52	30	79	84	6	43.5	46.8	8	0.84	0.85	−22	−16	18	20	4.02	4.61	

TABLE 1—*Concluded*

GROUP	CASE	DIAGNOSIS	SEX	AGE	WEIGHT	HEIGHT	BLOOD PRESSURE					PULSE RATE			TOTAL CALORIES PER HOUR			R. Q.		METABOLIC RATE		RESPIRATION RATE		VENTILATION RATE		NOTES
							Basal		Highest																	
							Systolic	Diastolic	Systolic	Diastolic	Percentage increase over basal in systolic	Basal	Highest	Percentage increase over basal	Basal	Highest	Percentage increase over basal	Basal	Highest	Basal	Highest	Basal	Highest	Basal	Highest	
					kgm.	*cm.*																				
13	261292	Neurasthenia	M	23	77.1	177.1	120	80	140	80	17	83	95	14	79.8	100.3	26	0.77	0.80	+4	+30	9	11	4.81	6.37	
	261292*	Neurasthenia			76.8		138	76	133	80	−4	99	108	9	97.7	116.4	19	0.80	0.87	+28	+52	12	10	5.74	7.70	Thyroxin 5 days previous to this test
	280559	Neurasthenia	F	26	46.3	151.3	106	76	120	68	13	88	104	18	56.3	62.3	11	0.71	0.77	+9	+21	18	20	4 42	5.15	
	257871	Neurasthenia	F	23	72.6	160.6	110	85	118	80	7	89	96	8	65.3	72.2	11	0.83	0.86	+1	+11	15	19	5.04	6.01	
	281027	Chronic nervous exhaustion	F	21	52.0	169.5	104	68	112	64	8	78	96	23	55.8	64.7	16	0.75	0.84	−5	+10	19	24	4.63	6.19	
	281509	Chronic nervous exhaustion	F	32	42.2	153.1	108	68	140	74	3	83	97	17	58.6	86.9	48	0.83	0.98	+20	+78	21	39	5.16	12.76	
14	165334	Normal control	M	22	70.5	174.7	118	78	142	78	20	77	104	35	79.7	99.3	25	0.73	0.89	+9	+36	12	18	4.95	7.44	
	263723	Normal control	M	47	68.8	175.0	128	80	140	70	9	67	84	25	79.5	88.7	12	0.82	0.81	+12	+25	18	17	6.20	6.74	
	263068	Normal control	M	37	67.8	172.9	130	82	140	70	8	84	88	5	70.0	85.3	22	0.90	0.83	−2	+19	19	16	7.11	8.69	
	263661	Normal control	M	25	70.5	178.3	104	65	124	74	19	60	73	22	79.3	94.6	19	0.77	0.82	+7	+27	16	21	5.44	7.69	

* The cases starred are omitted from the group averages given in Table 2.

cases of hyperthyroidism there was an increase of more than ten points in both the pulse and systolic blood pressure, while in the 6 normal soldiers on active duty the response in the pulse rate and systolic blood pressure was less definite.

Before the publication of the paper by Tompkins, Sturgis and Wearn, an investigation on the effect of the subcutaneous injection of adrenalin on the heat production, pulse rate, and blood pressure had been started in this laboratory; a preliminary report has recently been made (11) of the results given here in detail. The method of procedure was as follows: The patients came to the laboratory in the so-called post-absorptive condition and the basal metabolic rate, pulse rate, and blood pressure were determined after the patients had rested in bed twenty minutes according to the regular routine practiced in this laboratory and described in detail elsewhere (12). For the determination of the basal metabolic rate a mask is tightly adjusted over the patient's mouth and nose and, by means of expiratory and inspiratory valves, the total volume of the patient's expired air is collected in a gasometer for a known period of approximately ten minutes. Duplicate determinations are made of the carbon dioxid and oxygen content of the expired air, the analyses being done in the Haldane gas analysis apparatus. From the data obtained the basal metabolic rate is calculated by the usual method.

After the various basal values have been determined, 0.5 cc. of 1/1000 solution of adrenalin chlorid (Parke, Davis & Company) is injected subcutaneously in the patient's arm; the pulse and blood pressure are taken every five minutes for the next two hours and the metabolic rate determined for approximately ten-minute periods beginning about ten minutes, thirty minutes, one hour, and one and one-half hours after the injection.

Forty-six experiments were done on the 39 patients grouped according to diagnosis in table 1. The results of these experiments are summarized in table 2. Four experiments in group 1 are not included in the average given in table 2 because the dose of adrenalin was less than 0.5 cc.; 2 experiments in group 2, 1 in group 3, 1 in group 8, 2 in group 9 and 1 in group 13 are not included in the average because of previous thyroxin administration. The experiments omitted from the average are starred in table 1. The data obtained as basal before the adrenalin injection are contrasted in table 1 with the data which showed the most pronounced reaction following the injection. The percentage increase over the basal is given for the total calories, pulse rate, and systolic blood pressure. In table 2 are given the average data for the

various groups of cases studied. In table 3 are grouped those cases in which the adrenalin test was done both before and after the patients were given thyroxin.

TABLE 2

Summary of the effect of the subcutaneous injection of adrenalin chlorid on the systolic blood pressure, pulse rate, respiration rate, ventilation rate, respiratory quotient, total calories per hour and basal metabolic rate (standard dose of adrenalin chlorid 0.5 cc.)

GROUP	NUMBER OF CASES	DIAGNOSIS	AVERAGE B. M. R. FOR EACH GROUP	PERCENTAGE VARIATIONS FROM BASAL			NUMERICAL VARIATIONS FROM BASAL			
				Systolic blood pressure	Pulse rate	Total calories per hour	Respiration rate	Ventilation rate: liters S. T. P. D.	Respiratory quotient	Metabolic rate
			per cent	*per cent*	*per cent*	*per cent*				
1	9	Exophthalmic goiters; five with B. M. R. above +50 per cent	+68	18	25	22	5	2.82	0.12	38
2		Four with B. M. R. below +50 per cent	+15	14	11	15	2	1.35	0.04	17
		Average of all exophthalmic goiters	+44	16	18	19	4	2.17	0.08	29
3	3	Adenomas of thyroid; hyperthyroidism	+15	10	44	24	3	2.40	0.12	27
4	1	Double oöphorectomized neurasthenic with hyperthyroidism	+15	14	51	33	6	5.38	0.11	38
5	1	Adenoma of thyroid without hyperthyroidism	+4	−6	27	11	0	1.07	0.06	11
6	1	Colloid goiter; hypothyroidism	−16	14	26	28	5	1.51	−0.02	25
7	2	Addison's disease	−6	7	0	16	1	0.55	−0.03	15
8	3	Hypopituitarism	−16	4	21	14	4	1.84	0.16	12
9	2	Myxedema	−35	9	1	10	1	0.37	0.01	7
10	2	Postoperative myxedema	−16	0	12	29	−3	1.74	0.10	25
11	1	Atypical hypothyroidism on thyroxin	+10	8	48	42	3	1.85	0.11	45
12	1	Anorexia nervosa; hypothyroidism	−22	30	6	8	2	0.59	0.01	6
13	5	Neurasthenia and chronic nervous exhaustion	+6	10	16	22	6	2.48	0.07	24
14	4	Normal clinical controls	+7	14	22	20	2	1.72	0.03	20

DISCUSSION OF RESULTS

Heat production. In every experiment there was an increase in the heat production after the subcutaneous injection of adrenalin chlorid, the maximum occurring as a rule within ten to thirty minutes after the

injection. With but three exceptions, one patient with severe exophthalmic goiter in whom only 0.1 cc. adrenalin was injected, one patient with hypopituitarism, and one patient with anorexia nervosa, this maximum increase was at least 10 per cent above the basal; the greatest reaction was 48 per cent above the basal and occurred in a case of chronic nervous exhaustion. Within one and one-half to two hours after the adrenalin was injected the metabolic rate had returned to within 4 points of the preliminary level in 21 experiments; it was still somewhat elevated in 19 experiments, and it was slightly lower than the basal

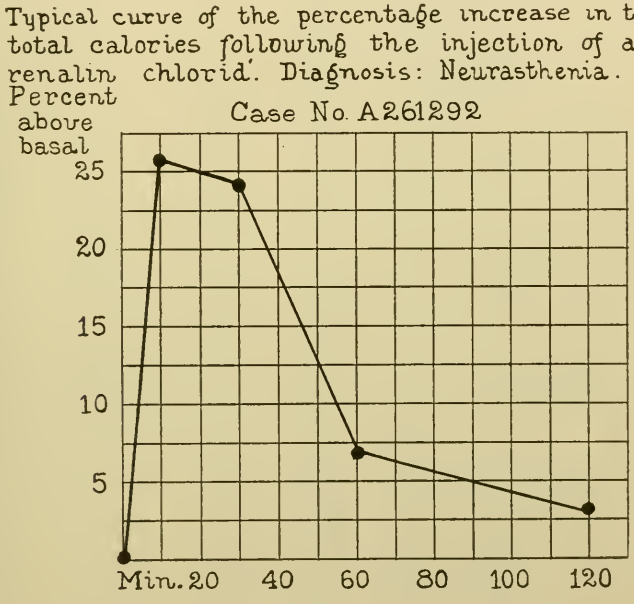

FIG. 1

determined before the injection in the remaining 6 experiments. A typical example of the post-adrenalin metabolic curve is given in figure 1.

In the group of patients with exophthalmic goiter with basal metabolic rates above +50 per cent who were given the standard dose of adrenalin the total number of calories per hour increased on the average 22 per cent over the basal, while in the group of patients with a milder degree of exophthalmic goiter whose basal metabolic rates were less than +50 per cent the total number of calories increased on the average 15 per cent. In spite of this no consistent relationship can be seen in the

TABLE 3

The effect of the subcutaneous injection of adrenalin chlorid, both before and after the intravenous injection of thyroxin, on the blood pressure, pulse rate, respiration rate, ventilation rate, respiratory quotient, total calories per hour and basal metabolic rate (standard dose of adrenalin chlorid 0.5 cc.)

CASE	DIAGNOSIS	BLOOD PRESSURE					PULSE RATE			TOTAL CALORIES PER HOUR			R. Q.		METABOLIC RATE		RESPIRATION RATE		VENTILATION RATE LITERS—S. T. P. D.		NOTES
		Basal		Highest																	
		Systolic	Diastolic	Systolic	Diastolic	Percentage increase over basal in systolic	Basal	Highest	Percentage increase over basal	Basal	Highest	Percentage increase over basal	Basal	Highest	Basal	Highest	Basal	Highest	Basal	Highest	
262089	Exophthalmic goiter...	128	78	138	85	8	104	112	8	77.4	85.1	10	0.67	0.76	+18	+30	20	22	5.45	7.07	
		120	78	141	77	18	104	112	8	75.6	90.8	20	0.72	0.82	+17	+40	22	26	5.84	7.39	8 mgm. thyroxin 5 days previous to test
261192	Exophthalmic goiter..	120	80	146	68	22	97	107	10	68.2	79.5	17	0.81	0.82	+13	+32	22	32	6.00	7.66	
		128	80	154	86	20	105	135	29	73.8	88.2	20	0.84	0.96	+22	+46	28	34	7.50	9.38	8 mgm. thyroxin 5 days previous to test
245549	Adenomas of thyroid; hyperthyroidism....	135	80	148	82	10	84	144	71	83.9	103.4	23	0.84	0.96	+20	+48	17	16	6.40	8.32	
		136	65	154	66	13	96	116	21	81.1	97.9	21	0.80	0.93	+16	+41	18	22	5.79	7.98	8 mgm. thyroxin 7 days previous to test
261342	Hypopituitarism.....	90	64	96	62	7	62	68	10	63.4	72.0	14	0.72	0.77	−13	−1	16	18	4.58	6.17	
		116	78	118	66	2	58	90	55	68.2	82.9	22	0.65	0.85	−5	+16	16	18	4.20	7.00	5 mgm. thyroxin 6 days previous to test
262555	Myxedema.....	114	88	122	70	7	60	59	−2	42.9	47.2	10	0.83	0.85	−40	−34	10	13	3.25	3.66	
		128	80	160	90	25	64	79	23	64.4	79.2	23	0.79	0.88	−7	+15	16	18	5.06	6.23	5 mgm. thyroxin 7 days previous to test
261292	Neurasthenia.....	120	80	140	80	17	83	95	14	79.8	100.3	26	0.77	0.80	+4	+30	9	11	4.81	6.37	
		138	76	133	80	−4	99	108	9	97.7	116.4	19	0.80	0.87	+28	+52	12	10	5.74	7.70	5 mgm. thyroxin 5 days previous to test

various groups studied and summarized in table 2, between the height of the adrenalin reaction and the degree of hyperthyroidism or hypothyroidism as determined by the level of the metabolic rate. This inconsistency is further shown in the 6 cases, (table 3) in which the adrenalin reaction was studied both before and after the intravenous injection of thyroxin for in two of these the percentage increase in the total calories after the adrenalin injection was less instead of greater in the adrenalin test carried out after the patients had received thyroxin. Furthermore, there is only a very slight difference in the average increase in the heat production from the adrenalin injection before thyroxin was administered (17 per cent) as compared with the average increase after thyroxin was given (21 per cent).

The metabolic curve resulting from the subcutaneous injection of adrenalin is entirely different from that found by Plummer following the intravenous injection of 16 mg. of thyroxin. Following the injection of adrenalin the height of the metabolic curve is reached in approximately from ten to thirty minutes and has returned to its basal level in about two hours; when thyroxin is injected, however, the height is not reached for approximately from three to ten days and the basal level not regained for from one to two months. The presence of hyperglycemia (13) following the injection of adrenalin chlorid naturally directs attention to the similarity of the post-adrenalin metabolic curve to that found by Lusk (14) as a result of carbohydrate plethora following the ingestion of glucose.

Ventilation and respiration rates. There is invariably an increase in the ventilation rate following the injection of adrenalin chlorid and this is usually accompanied by an increase in the respiration rate, although there may even be a decrease in the latter. The variations in the percentages of carbon dioxid eliminated in the expired air and of oxygen absorbed from the inspired air vary inversely with the changes in the ventilation rate and directly with the increase in the metabolism. It is impossible, however, to predict the degree with which the increase in the respiratory volume will predominate over the concentration of that volume in different individuals or even in the same individual at different times.

Respiratory quotient. Following the injection of adrenalin there was an increase in the respiratory quotient in 39 experiments, no change in 1 experiment, and a decrease in 6. These results taken in conjunction with those of Tompkins, Sturgis and Wearn (6) indicate that as a rule there is an increase in carbohydrate combustion; this is confirmed by

the findings of other observers of an increase in the blood sugar (13) following the injection of adrenalin. The action of adrenalin, therefore, is not only to cause a higher rate of oxidation but also to mobilize carbohydrate as fuel for this increased combustion; which reaction is primary is not known.

Diastolic blood pressure. Throughout the groups there is no constant variation in the diastolic blood pressure. In 19 experiments there was an increase, in 7 there was no change, and in 20 there was a decrease. If the peripheral capillary cross section remains constant when the blood flow is increased the diastolic blood pressure necessarily rises; an unchanged or decreased diastolic with increased blood flow would indicate a compensatory peripheral dilatation. Even a certain proportion of those experiments that showed a slight increase in diastolic blood pressure may likewise have had a slight peripheral dilatation that was not, however, of sufficient degree entirely to compensate for the increased blood flow. A peripheral compensatory dilatation is, therefore, indicated by the data in 27 experiments; it may have occurred in an unknown proportion of the other 19 experiments. Further evidence of peripheral dilatation is shown by the flushing of the skin and increased perspiration, which are physical compensatory factors to accommodate the body to the increased production of heat.

Systolic blood pressure. An increase in the systolic blood pressure was noted in all but 4 cases following the adrenalin injection. These four are as follows: One case of adenomas of the thyroid without hyperthyroidism with a basal metabolic rate of +4 per cent; one case of hypopituitarism with a basal metabolic rate of −28 per cent; one case of post-operative myxedema with a basal metabolic rate of −13 per cent; and one case of neurasthenia with a rate of +28 per cent after an injection of thyroxin. In 18 cases the increase was less than 10 per cent; in 17 the increase was between 10 per cent and 20 per cent, and in 7 the increase was 21 per cent or more above the basal. From a study of the individual experiments, of the averages of the various groups of patients, or of the experiments carried out after the patients had received thyroxin, no consistent parallelism can be seen between the percentage increase in the systolic blood pressure following the injection of adrenalin and the degree of over- or under-activity of the thyroid gland.

Pulse rate. The pulse rate increased in all but 3 cases: One of these was a case of myxedema in which the basal metabolic rate was − 40 per cent; the second, a case of Addison's disease in which the basal

metabolic rate was −3 per cent; and the third, a case of mild exophthalmic goiter in a stage of remission in which the basal metabolic rate was + 9 per cent. Ten cases showed less than a 10 per cent increase; all the rest showed a greater response. With an increase in the oxygen consumed and carbon dioxid produced following the injection of adrenalin the circulatory system must transport larger amounts of these and of other substances. This can be accomplished in two ways: *a*, by an increase (15), (16) in the blood flow which can be brought about either by an increase in the number of beats of the heart for each minute, or by an increase in the volume of each beat (or by both, or by a large increase of one with a decrease of the other); and *b*, by a unit volume

TABLE 4

Summary of effect of subcutaneous injection of adrenalin chlorid on blood pressure, pulse rate, and respiration rate (standard dose of adrenalin chlorid 0.5 cc.)

NUMBER OF CASES	DIAGNOSIS	AVERAGE B. M. R.	PERCENTAGE INCREASE OVER BASAL	
			Systolic blood pressure	Pulse
		per cent	*per cent*	*per cent*
8	Exophthalmic goiter	+32	14	18
6	Adenomas of thyroid with hyperthyroidism	+30	17	11
4	Adenomas of thyroid without hyperthyroidism	−1	7	14
2	Colloid goiter	+3	3	17
4	Cardiac disease	+2	13	25
3	Neurasthenia	+4	6	15
1	Malignancy	−3	3	21
1	Pulmonary tuberculosis	+20	18	6

of blood carrying a greater load. Which of these variable factors will predominate is of course impossible to predict. Furthermore, no consistent relationship can be seen following the injection of adrenalin between the response of the pulse rate and the degree of activity of the thyroid gland.

Supplementary experiments. A second series of 29 experiments was carried out in a manner similar to that employed in the preceding series except that the metabolic rates were not determined after the administration of adrenalin. The results are presented in a summarized form in table 4. As in the first series, there is in the various groups an average irregular increase in both pulse rate and systolic blood

pressures. We can discern no parallelism between the changes in pulse rate and blood pressures and the degree of hyperthyroidism that would in any way render the reaction of diagnostic value in such conditions, as has been suggested by Goetsch (17).

GENERAL DISCUSSION

These experiments indicate that the injection of adrenalin chlorid produces invariably an increase in the rate of cellular combustion varying between a calorific increase of from 4 per cent to 48 per cent. This increase is accompanied as a rule by an increase in the ventilation rate, respiration rate, number of heart beats for each minute, volume of each beat, greater utilization of the blood-carrying power and peripheral dilatation with an increased systolic and decreased diastolic blood pressure. Not all these compensatory factors necessarily come into play in each instance; as would be expected, various combinations may occur, sometimes one factor, sometimes another factor acting as the major compensation. In individual instances it is impossible to predict the combination, although in perfectly healthy and well-trained persons such as those in the group of normal soldiers studied by Tompkins, Sturgis and Wearn, each compensation factor plays its rôle so well and so easily that there is discernible only the slightest increase of any one factor, while in the case of ill-acting hearts (irritable hearts) the response to extra demands is not smoothly and efficiently accomplished. This is true also in any condition like hyperthyroidism in which the circulatory system is more or less damaged and already severely taxed by its own increased metabolism, and as a result an additional load is not readily borne.

No relationship was found in our experiments between the intensity of the reaction and the degree of hyper- or hypothyroidism. There is no sound physiologic foundation, so far as we can see, for the assumption that the character of the reaction following the injection of adrenalin chlorid is indicative of the activity of the thyroid gland.

The cause of the increased heat production is unknown. The similarity of the metabolic rate curve following the injection of adrenalin to that found by Lusk from a carbohydrate plethora naturally directs attention to the possibility that the increased heat production is due to an excess of carbohydrate metabolites. In addition there may be, however, a direct chemical stimulation of cellular combustion. In either case the phenomenon is obviously in harmony with Cannon's (18) "emergency theory" of the action of adrenalin.

SUMMARY

1. Forty-six experiments are reported on the effect of the subcutaneous injection of adrenalin chlorid on the metabolic rate, pulse rate, and blood pressure of patients suffering from various disorders of the ductless glands.

2. A supplementary series of 27 experiments is added in which a study was made of the effect of the adrenalin injection on the pulse rate, and blood pressure (the basal metabolic rate being known).

3. Adrenalin chlorid (0.5 cc. of 1 1000) injected subcutaneously invariably causes an increase in the metabolic rate. This increase is usually accompanied by an increase in the ventilation rate, respiration rate, number of heart beats each minute, volume of each beat, greater utilization of the blood carrying power and peripheral dilatation with an increased systolic and decreased diastolic blood pressure.

4. No relationship was found between the intensity of the adrenalin reaction and the degree of hyperthyroidism or hypothyroidism.

5. Attention is directed to the similarity of the metabolic rate curve following the injection of adrenalin to that found by Lusk from a carbohydrate plethora and to the possibility that the increased heat production is due to an excess of carbohydrate metabolites. It is suggested that in addition there may be a direct stimulation of cellular combustion.

BIBLIOGRAPHY

(1) Fuchs and Roth: Zeitschr. f. exper. Path. u. Therap., 1911–12, x, 187.
(2) Hari: Biochem. Zeitschr., 1912, xxxviii, 23.
(3) Bernstein and Falta: Verhandl. d. Deutsch. Kong. f. Innere Med., 1912, 536.
(4) Lusk: Proc. Internat. Cong. Med., 1913, xiii.
(5) Lusk and Riche: Arch. Int. Med., 1914, xiii, 673.
(6) Tompkins, Sturgis and Wearn: Arch. Int. Med., 1919, xxiv, 269.
(7) La Franca: Zeitschr. f. exper. Path. u. Therap., 1909, vi, 1.
(8) Wilenko: Biochem. Zeitschr., 1912, xlii, 44.
(9) Bernstein: Zeitschr. f. exper. Path. u. Therap., 1914, xv, 86.
(10) Jackson: Journ. Lab. Clin. Med., 1916, ii, 145.
(11) Boothby and Sandiford: Proc. Amer. Physiol. Soc., This Journal, 1920, li, 200-201.
(12) Boothby and Sandiford: Laboratory manual on the technic of basal metabolic rate determinations, Philadelphia, Saunders, (in press).
(13) Cannon: Bodily changes in pain, hunger, fear and rage, New York, Appleton, 1915.
(14) Lusk: Science of nutrition, Philadelphia, Saunders, 1917.

(15) Boothby: This Journal, 1915, xxxvii, 383.
(16) Boothby and Sandiford: This Journal, 1916, xl, 547.
(17) Goetsch: N. Y. State Journ. Med., 1918, xviii, 259.
(18) Cannon: This Journal, 1919, l, 399.

QP171 Sa52
Sandiford
Clinical metabolism
APR 5 1946

COLUMBIA LIBRARIES OFFSITE
HEALTH SCIENCES STANDARD
HX64136434
QP171 .Sa52 Clinical metabolism:
RECAP